General

Guideline Title

IWGDF guidance on the diagnosis and management of foot infections in persons with diabetes.

Bibliographic Source(s)

Lipsky BA, AragÃ³n-SÃ¡nchez J, Diggle M, Embil J, Kono S, Lavery L, Senneville Ã‰, Urbancic-Rovan V, Van Asten S, Peters EJ, International Working Group on the Diabetic Foot. IWGDF guidance on the diagnosis and management of foot infections in persons with diabetes. Diabetes Metab Res Rev. 2016 Jan;32(Suppl 1):45-74. [270 references] PubMed

Guideline Status

This is the current release of the guideline.

This guideline meets NGC's 2013 (revised) inclusion criteria.

Regulatory Alert

FDA Warning/Regulatory Alert

Note from the National Guideline Clearinghouse: This guideline references a drug(s) for which important revised regulatory and/or warning information has been released.

- May 12, 2016 – Fluoroquinolone antibacterial drugs: The U.S. Food and Drug Administration (FDA) is advising that the serious side effects associated with fluoroquinolone antibacterial drugs generally outweigh the benefits for patients with sinusitis, bronchitis, and uncomplicated urinary tract infections who have other treatment options. For patients with these conditions, fluoroquinolones should be reserved for those who do not have alternative treatment options.

Recommendations

Major Recommendations

Note from the National Guideline Clearinghouse (NGC) and the International Working Group on the Diabetic Foot (IWGDF): For the 2015 IWGDF Guidance documents, the IWGDF invited five working groups of international experts to produce guidance on the prevention and management of foot problems in diabetes. Major recommendations provided in the *IWDDF guidance on the diagnosis and management of foot infections in persons with diabetes* are presented below. See also the NGC summaries of IWGDF guidance on the following related topics:

- Prevention of foot ulcers in at-risk patients with diabetes
- Footwear and offloading to prevent and heal foot ulcers in diabetes
- Diagnosis, prognosis, and management of peripheral artery disease in patients with foot ulcers in diabetes
- Interventions to enhance healing of chronic ulcers of the foot in diabetes

Definitions for the quality of the evidence (High, Moderate, Low, Very Low) and strength of recommendations (Strong, Weak) are provided at the end of the "Major Recommendations" field.

Diagnosis and Classification

1. Diabetic foot infection must be diagnosed clinically, based on the presence of local and systemic signs and symptoms of inflammation (Grading of Recommendations Assessment, Development and Evaluation [GRADE] recommendation: Strong; Quality of evidence: Moderate).
2. Assess the severity of any diabetic foot infection (DFI) using the Infectious Diseases Society of America (IDSA)/IWGDF classification scheme (Strong; Moderate).

Osteomyelitis

3. For an infected open wound, perform a probe-to-bone test; in a patient at low risk for osteomyelitis, a negative test largely rules out the diagnosis, while in a high-risk patient, a positive test is largely diagnostic (Strong; High).
4. Markedly elevated serum inflammatory markers, especially erythrocyte sedimentation rate, are suggestive of osteomyelitis in suspected cases (Weak; Moderate).
5. A definite diagnosis of bone infection usually requires positive results on both histological (and optimally microbiological) examinations of an aseptically obtained bone sample, but this is usually required only when the diagnosis is in doubt or determining the causative pathogen's antibiotic susceptibility is crucial (Strong; Moderate).
6. A probable diagnosing of bone infection is reasonable if there are positive results on a combination of diagnostic tests, such as probe-to-bone, serum inflammatory markers, plain X-ray, magnetic resonance imaging (MRI) or radionuclide scanning (Strong; Weak).
7. Avoid using results of soft tissue or sinus tract specimens for selecting antibiotic therapy for osteomyelitis as they do not accurately reflect bone culture results (Strong; Moderate).
8. Obtain plain X-rays of the foot in all cases of non-superficial DFI (Strong; Low).
9. Use MRI when an advanced imaging test is needed for diagnosing diabetic foot osteomyelitis (DFO) (Strong; Moderate).
10. When MRI is not available or contraindicated, consider a white blood cell-labelled radionuclide scan, or possibly single-photon emission computed tomography (CT) and computed tomography (SPECT/CT) or fluorine-18-fluorodeoxyglucose positron emission tomography (PET) scans (Weak; Moderate).

Assessing Severity

11. At initial evaluation of any infected foot, obtain vital signs and appropriate blood tests, debride the wound and probe and assess the depth and extent of the infection to establish its severity (Strong; Low).
12. At initial evaluation, assess arterial perfusion and decide whether and when further vascular assessment or revascularization is needed (Strong; Low).

Microbiological Considerations

13. Obtain cultures, preferably of a tissue specimen rather than a swab, of infected wounds to determine the identity of causative microorganisms and their antibiotic sensitivity (Strong; High).
14. Do not obtain repeat cultures unless the patient is not clinically responding to treatment, or occasionally for infection control surveillance of resistant pathogens (Strong; Low).
15. Send collected specimens to the microbiology laboratory promptly, in sterile transport containers, accompanied by clinical information on the type of specimen and location of the wound (Strong; Low).

Treatment

Surgical

16. Consult a surgical specialist in selected cases of DFIs that are moderate and in all cases that are severe (Weak; Low).
17. Performing urgent surgical intervention is necessary in most cases of deep abscesses, compartment syndrome and virtually all necrotizing soft tissue infections (Strong; Low).

18. Considering surgical intervention is usually advisable in cases of osteomyelitis accompanied by spreading soft tissue infection, destroyed soft tissue envelope, progressive bone destruction on X-ray or bone protruding through the ulcer (Strong; Low).

Antimicrobial Therapy

19. While virtually all clinically infected diabetic foot wounds require antimicrobial therapy, do not treat clinically uninfected diabetic foot wounds with antimicrobial therapy (Strong; Low).
20. Select specific antibiotic agents for treatment based on the likely or proven causative pathogens, their antibiotic susceptibilities, the clinical severity of the infection, evidence of efficacy for DFI and costs (Strong; Moderate).
21. A course of antibiotic therapy of 1 to 2 weeks is usually adequate for most soft tissue DFIs (Strong; High).
22. Administer parenteral therapy initially for most severe infections and some moderate infections, with a switch to oral therapy when the infection is responding (Strong; Low).

Wound Care

23. Do not select a specific type of dressing for a DFI with the aim of preventing an infection, or improving its outcome (Strong; High).

Treating Osteomyelitis

24. For DFO, the IWDGF Working Group recommends 6 weeks of antibiotic therapy for patients who do not undergo resection of infected bone and no more than a week of antibiotic therapy if all infected bone is resected (Strong; Moderate).

Adjunctive Therapies

25. The IWGDF Working Group suggests not using any adjunctive treatments for DFI (Weak; Low).

Issues of Particular Importance in Developing (Low-Income) Countries

26. When treating a DFI, assess for use of traditional remedies and previous antibiotic use and consider local bacterial pathogens and their susceptibility profile (Strong; Low).

Definitions

Recommendations in this guidance were formulated based on the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system for grading evidence when writing a clinical guideline. The authors assessed the quality of evidence on the risk of bias of included studies, effect sizes, and expert opinion, and rated the quality of evidence as 'high,' 'moderate' or 'low.' They assessed the strength of each recommendation as 'strong' or 'weak,' based on the quality of evidence, balance between benefits and harm, patient values and preferences, and costs (resource utilization). The rationale behind each recommendation is described in the original guideline document. See the GRADE Web site for more information.

Clinical Algorithm(s)

An algorithm titled "Algorithm overview of the approach to the patient with diabetes and a foot infection" is provided in the original guideline document.

Scope

Disease/Condition(s)

Diabetic foot infections including osteomyelitis

Guideline Category

Diagnosis

Evaluation

Management

Treatment

Clinical Specialty

Endocrinology

Family Practice

Infectious Diseases

Internal Medicine

Pathology

Podiatry

Intended Users

Advanced Practice Nurses

Nurses

Physician Assistants

Physicians

Podiatrists

Guideline Objective(s)

To provide recommendations for the diagnosis and management of foot infections in persons with diabetes

Target Population

Persons aged 18 years and older with suspected or confirmed diabetic foot infections

Interventions and Practices Considered

Diagnosis/Evaluation

1. Clinical diagnosis based on the presence of local or systemic signs or symptoms of inflammation
2. Assessing the severity of diabetic foot infection using the Infectious Diseases Society of America/International Working Group on the Diabetic Foot (IWGDF) classification scheme
3. Performing a probe-to-bone test for osteomyelitis
4. Testing for elevated serum inflammatory markers, especially erythrocyte sedimentation rate
5. Microbiological and histological examinations of an aseptically obtained bone sample
6. Imaging (plain X-ray, magnetic resonance imaging [MRI], white blood cell-labelled radionuclide scanning, single-photon emission computed tomography [CT] and CT [SPECT/CT] or fluorine-18-fluorodeoxyglucose positron emission tomography/CT scans)
7. Using results of soft tissue or sinus tract specimens for selecting antibiotic therapy for osteomyelitis (not recommended)
8. Debriding the wound and probing and assess the depth and extent of the infection to establish its severity
9. Blood tests and assessment of vital signs
10. Assessment of arterial perfusion
11. Obtaining cultures of infected wounds to determine the causative microorganisms and their antibiotic sensitivity

Treatment/Management

1. Surgical treatment
2. Antimicrobial therapy (for clinically infected wounds only)
    - Selection of specific antibiotic agents for treatment
    - Duration of antibiotic therapy
    - Parenteral versus oral therapy
3. Wound care
4. Treating osteomyelitis
5. Use of adjunctive treatments (not recommended)
6. Consideration of issues of particular importance in developing (low-income) countries

Major Outcomes Considered

- Effectiveness of surgical and antimicrobial treatments
- Wound healing
- Infection control
- Clinical cure rate or clinical improvement rate
- Bacteriological success rate (microbiological outcomes)
- Amputation rate
- Infection recurrence rate
- Days of hospitalizations (length of stay)
- Adverse events

Methodology

Methods Used to Collect/Select the Evidence

Searches of Electronic Databases

Description of Methods Used to Collect/Select the Evidence

The methods used in the systematic review (see the "Availability of Companion Documents" field) for this guideline were identical to those used for a previous systematic review of this topic. The PubMed and Excerpta Medica (EMBASE) databases were searched using the string described in Online Appendix A that was designed to identify all prospective and retrospective studies, in any language, that evaluated interventions for the treatment of foot infections in people aged 18 years or older who had diabetes mellitus, and which were published before 30 June 2014. Eligible studies included randomized controlled trials (RCTs), case–control studies, prospective and retrospective cohort studies, interrupted time series (ITS) or controlled before-and-after (CBA) design studies. Studies in which subjects with diabetic foot infections (DFIs) formed part of the total population were only included if the data for the subgroup with diabetes were separately described. Case series, uncontrolled case series and studies with non-concurrent controls were excluded, as were studies that were not related to treatment of DFIs.

One author assessed each study identified by the search string, based on the title and abstract, to see if it met the eligibility criteria. For potentially eligible publications, pairs of authors independently reviewed the full, published article to assess whether or not it met the eligibility criteria. If the two reviewers disagreed, they worked to reach consensus, with input from a third reviewer, if necessary.

Number of Source Documents

The literature search identified a total of 13,365 articles (6292 from PubMed and 7073 from EMBASE), of which 5848 were published between July 2010 and July 2014. Figure 1 of the systematic review (see the "Availability of Companion Documents" field) summarizes the flow diagram of the review process of all articles published by June 2014. After review of all titles and abstracts, 567 articles were selected for full text review. Of these, only 35 met the eligibility criteria for inclusion. Five additional studies identified by means other than the literature search were added, one of

which was published between 2010 and 2014.

Methods Used to Assess the Quality and Strength of the Evidence

Weighting According to a Rating Scheme (Scheme Given)

Rating Scheme for the Strength of the Evidence

Recommendations in the guidance were formulated based on the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system for grading evidence when writing a clinical guideline. The authors assessed the quality of evidence on the risk of bias of included studies, effect sizes, and expert opinion, and rated the quality of evidence as 'high', 'moderate' or 'low'. See the GRADE Web site for more information.

Methods Used to Analyze the Evidence

Review of Published Meta-Analyses

Systematic Review with Evidence Tables

Description of the Methods Used to Analyze the Evidence

Using specially prepared forms, the groups of reviewers recorded study design, characteristics of subject populations, details of interventions, study outcomes and the duration of follow-up. Investigators scored all studies for methodological quality using scoring lists developed by the Dutch Cochrane Centre. Quality items were rated as 'done', 'not done' or 'not reported', with only those rated as 'done' contributed to the methodological quality score. When scoring the study design, authors applied equal weighting to each validity criterion.

The methodological quality score was translated into a level of evidence using the Scottish Intercollegiate Guidelines Network instrument as either level 1 (randomized controlled trials) or level 2 (case-control, cohort, controlled before-and-after [CBA] or interrupted time series [ITS] studies). Studies were also rated as follows: ++ (high quality with low risk of bias); + (well conducted with low risk of bias); or − (low quality with higher risk of bias). Co-reviewers worked to reach agreement on the findings from the data extraction and the evaluation of methodological quality of each article and described each study on a narrative basis. Because of the heterogeneity of study designs, interventions, follow-up and outcomes, we made no attempt to pool the results of the included studies. The evidence tables were compiled following collective discussion.

Methods Used to Formulate the Recommendations

Expert Consensus

Description of Methods Used to Formulate the Recommendations

Following the systematic review, the experts in the working group formulated recommendations based on the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system for grading evidence when writing a clinical guideline. The GRADE system allows the experts to provide a rating for each recommendation based on both the strength with which it is recommended and the quality of the evidence underlying it. In this manner the link is made between scientific evidence and recommendations for daily clinical practice (see the "Rating Scheme for the Strength of the Recommendations" field).

Rating Scheme for the Strength of the Recommendations

Recommendations in the guidance were formulated based on the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system for grading evidence when writing a clinical guideline. The authors assessed the strength of each recommendation as 'strong' or 'weak', based on the quality of evidence, balance between benefits and harm, patient values and preferences, and costs (resource utilization). See the GRADE Web site for more information.

Cost Analysis

The systematic review identified two studies that compared economic aspects of different antibiotic regimens in the treatment of soft tissue diabetic foot infections (DFIs). In one, among subjects admitted to hospital, the authors reported a total potential cost saving of $US61 per subject treated with once-daily ceftriaxone and metronidazole compared with four times daily ticarcillin/clavulanate. In the second study, a subgroup analysis of a larger randomized controlled trial (RCT), the authors performed a cost-minimization assessment comparing treatment with ertapenem versus piperacillin/tazobactam. Because piperacillin/tazobactam requires more frequent dosing for drug preparation and administration, were higher. The difference in cost per patient per day was, however, only about $US6.

Method of Guideline Validation

Internal Peer Review

Description of Method of Guideline Validation

Consensus

The members of the International Working Group on the Diabetic Foot (IWGDF) Editorial Board met in person on a number of occasions to thoroughly review the systematic reviews and the Guidance documents, which were then revised by the working group based on this editorial review. When found satisfactory, the Editorial Board sent the Guidance document to the IWGDF representatives for comments; the editorial board processed all comments received and made changes where needed in collaboration with the chair of the working group.

Evidence Supporting the Recommendations

Type of Evidence Supporting the Recommendations

The type of supporting evidence is identified and graded for each recommendation (see the "Major Recommendations" field).

Benefits/Harms of Implementing the Guideline Recommendations

Potential Benefits

In recent decades, as the prevalence of diabetes has increased, so too have foot complications, including infections. The development of a foot infection is associated with substantial morbidity, including discomfort, reduced physical and mental quality of life, need for healthcare provider visits, wound care, antimicrobial therapy and often surgical procedures. Furthermore, foot infection remains the most frequent diabetic complication requiring hospitalization and the most common precipitating event leading to lower extremity amputation. Managing infection requires careful attention to properly diagnosing the condition, obtaining appropriate specimens for culture, thoughtfully selecting empirical and then definitive antimicrobial therapy, quickly determining when surgical interventions are needed and providing all other necessary types of wound care. For these reasons, interdisciplinary teams should, whenever possible, include an infectious diseases or clinical microbiology specialist. A systematic and, to the extent possible, evidence-based approach to diabetic foot infections (DFIs) should result in better outcomes.

Refer to the "Rationale" sections in the original guideline document for an assessment of balance of benefits and harms for each recommendation.

Potential Harms

- Failure to treat an infected diabetic foot wound with antimicrobial therapy is usually associated with progressive tissue destruction and poor wound healing. However, antibiotic therapy is associated with frequent adverse effects, financial costs and increasing the risk of antibiotic resistance, so it should be reserved for treating wounds that are infected.

- Fluoroquinolones are associated with an increased risk of adverse effects, including *Clostridium difficile* disease, and failure with one of these agents may cause resistance to others.
- One new agent, tigecycline (which has broad-spectrum activity, including against methicillin-resistant *Staphylococcus aureus* [MRSA]), when compared with ertapenem (with or without vancomycin) was found in a recent large, multicenter, randomized controlled trial to be significantly inferior in clinical outcomes and to have a significantly higher rate of adverse effects.
- Complications of percutaneous bone biopsy, such as minimal bleeding (≤3%), introducing bacteria into bone or inducing a fracture or acute Charcot arthropathy, are extremely rare.
- Both histology and culture results of bone specimens may be misleading. False-positive results caused by skin contamination can be reduced by using a dorsal route in case of a plantar ulcer and by keeping a minimal distance of 20 mm from the ulcer periphery when introducing the biopsy needle. Culture of a bone specimen may be falsely negative because of sampling errors, prior antibiotic therapy or a failure to isolate fastidious organisms. Similarly, bone histopathology may be falsely negative because of sampling error or falsely positive in patients with some non-infectious inflammatory disorders.

Refer to the "Rationale" sections in the original guideline document for an assessment of balance of benefits and harms for each recommendation.

Contraindications

Contraindications

Magnetic resonance imaging is contraindicated in patients with a metal implant or claustrophobia.

Qualifying Statements

Qualifying Statements

Not stated

Implementation of the Guideline

Description of Implementation Strategy

Guidelines will be implemented via the training programs of the International Working Group on the Diabetic Foot (IWGDF) as well as with support of the translation of the guidelines in local languages.

Implementation Tools

Quick Reference Guides/Physician Guides

For information about availability, see the *Availability of Companion Documents* and *Patient Resources* fields below.

Institute of Medicine (IOM) National Healthcare Quality Report Categories

IOM Care Need

Getting Better

Living with Illness

IOM Domain

Effectiveness

Identifying Information and Availability

Bibliographic Source(s)

Lipsky BA, AragÃ³n-SÃ¡nchez J, Diggle M, Embil J, Kono S, Lavery L, Senneville Ã‰, Urbancic-Rovan V, Van Asten S, Peters EJ, International Working Group on the Diabetic Foot. IWGDF guidance on the diagnosis and management of foot infections in persons with diabetes. Diabetes Metab Res Rev. 2016 Jan;32(Suppl 1):45-74. [270 references] PubMed

Adaptation

Not applicable: The guideline was not adapted from another source.

Date Released

2016 Jan

Guideline Developer(s)

International Working Group on the Diabetic Foot - Nonprofit Organization

Source(s) of Funding

International Working Group on the Diabetic Foot

Guideline Committee

International Working Group on the Diabetic Foot

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Financial Disclosures/Conflicts of Interest

The International Working Group on the Diabetic Foot Guidance is developed by working groups of independent experts. These documents are

written without any influence from commercial, political, academic or other interest groups.

Conflicts of Interest

BAL: research funding from Innocoll; consulting for Innocoll, Merck, Pfizer, Dipexium, Cubist, Cerexa and KCI/Acelity.

LL: is on the speaker's bureau for Osiris, Integra, PamLabs and Smith & Nephew; consultant for KCI, PamLabs and Innovacyn; stock ownership in Prizm Medical; received research grants from Osiris, MacroCure, ThermoTrek, Integra, GlaxoSmithKline, KCI, Cardinal and Dipexium.

ES: speaker and received congress support from Sanofi-Aventis and Novartis; consulting and received congress support from Pfizer; consultant for Cubist.

JAS, MD, JE, SK, VUR, SVA and EJP: none declared.

Guideline Status

This is the current release of the guideline.

This guideline meets NGC's 2013 (revised) inclusion criteria.

Guideline Availability

Available from the Diabetes/Metabolism Research and Reviews Web site .

Availability of Companion Documents

The following are available:

- Peters EJ, Lipsky BA, Aragón-Sánchez J, Diggle M, Embil JM, Kono S, Lavery L, Senneville É, Urbancic-Rovan V, Van Asten SA. Interventions in the management of infection in the foot in diabetes: a systematic review. Diabetes Metab Res Rev. 2016 Jan;32(Suppl 1):145-53. Available from the Diabetes/Metabolism Research and Reviews Web site .
- Bakker K, Apvelqvist J, Lipsky BA, Van Netten JJ, Schaper NC, International Working Group on the Diabetic Foot (IWGDF). The 2015 IWGDF guidance documents on prevention and management of foot problems in diabetes: development of an evidence-based global consensus. Diabetes Metab Res Rev. 2016 Jan;32(Suppl 1):2-6. Available from the Diabetes/Metabolism Research and Reviews Web site .
- Schaper NC, Van Netten JJ, Apelqvist J, Lipsky BA, Bakker K, International Working Group on the Diabetic Foot (IWGDF). Prevention and management of foot problems in diabetes: a summary guidance for daily practice 2015, based on the IWGDF Guidance Documents. Diabetes Metab Res Rev. 2016 Jan;32(Suppl 1):7-15. Available from the Diabetes/Metabolism Research and Reviews Web site .

Patient Resources

None available

NGC Status

This NGC summary was completed by ECRI Institute on November 4, 2016. The information was verified by the guideline developer on December 11, 2016.

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